

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
16 December 2004 (16.12.2004)

PCT

(10) International Publication Number
WO 2004/108691 A1

(51) International Patent Classification⁷: **C07D 239/42**

(21) International Application Number:
PCT/GB2004/002373

(22) International Filing Date: 3 June 2004 (03.06.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0312896.4 5 June 2003 (05.06.2003) GB
0324793.9 24 October 2003 (24.10.2003) GB

(71) Applicant (for all designated States except US): **ASTRAZENECA UK LIMITED** [GB/GB]; 15 Stanhope Gate, London, Greater London W1K 1LN (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **CRABB, Jeffrey, Norman** [GB/GB]; AstraZeneca, Severn Road, Hallen, Bristol BS10 7ZE (GB). **HORBURY, John** [GB/GB]; AstraZeneca, Severn Road, Hallen, Bristol BS10 7ZE (GB). **TAYLOR, Nigel, Philip** [GB/GB]; AstraZeneca, Charter Way, Macclesfield, Cheshire SK10 2NA (GB).

(74) Agent: **ASTRAZENECA**; Global Intellectual Property, S-151 85 Sodertalje (SE).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

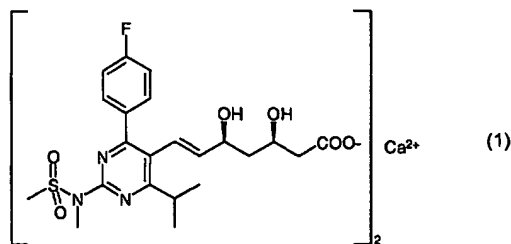
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: IMPROVED PRODUCTION OF ROSUVASTATIN CALCIUM SALT



(57) Abstract: An improved process for manufacture of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid calcium salt, Formula (1), which is useful for the production of a pharmaceutical useful in the treatment of, inter alia, hypercholesterolemia, hyperlipoproteinemia and atherosclerosis, is described.

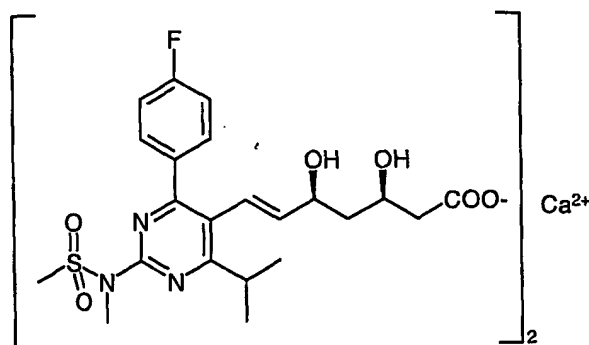
BEST AVAILABLE COPY

WO 2004/108691 A1

IMPROVED PRODUCTION OF ROSUVASTATIN CALCIUM SALT

This invention concerns improvements to a chemical process, particularly a chemical process for manufacture of (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-

5 [methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid calcium salt (1) (illustrated below), which is useful for the production of a pharmaceutical useful in the treatment of, inter alia, hypercholesterolemia, hyperlipoproteinemia and atherosclerosis.

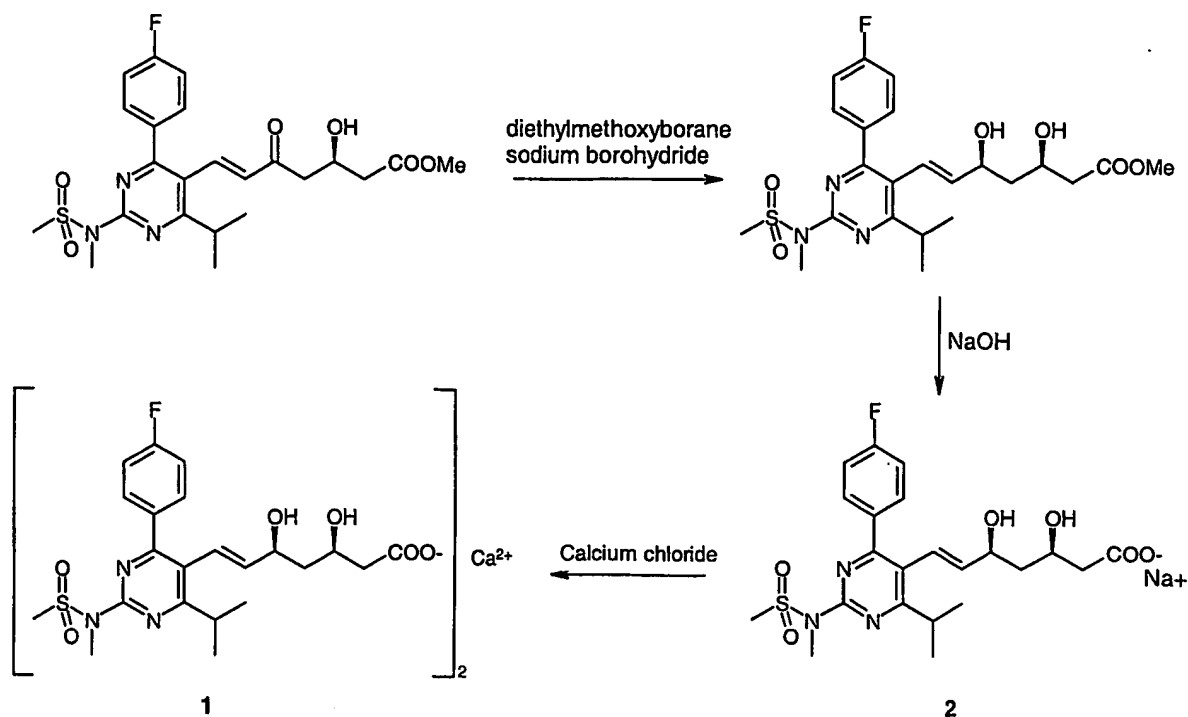


1

The sodium salt (2) and calcium salt (1) of compound (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-

1 enoic acid (hereinafter referred to as the 'Agent') were disclosed in European Patent 0521471. This patent also describes a process for the synthesis of the calcium salt (1), via the sodium

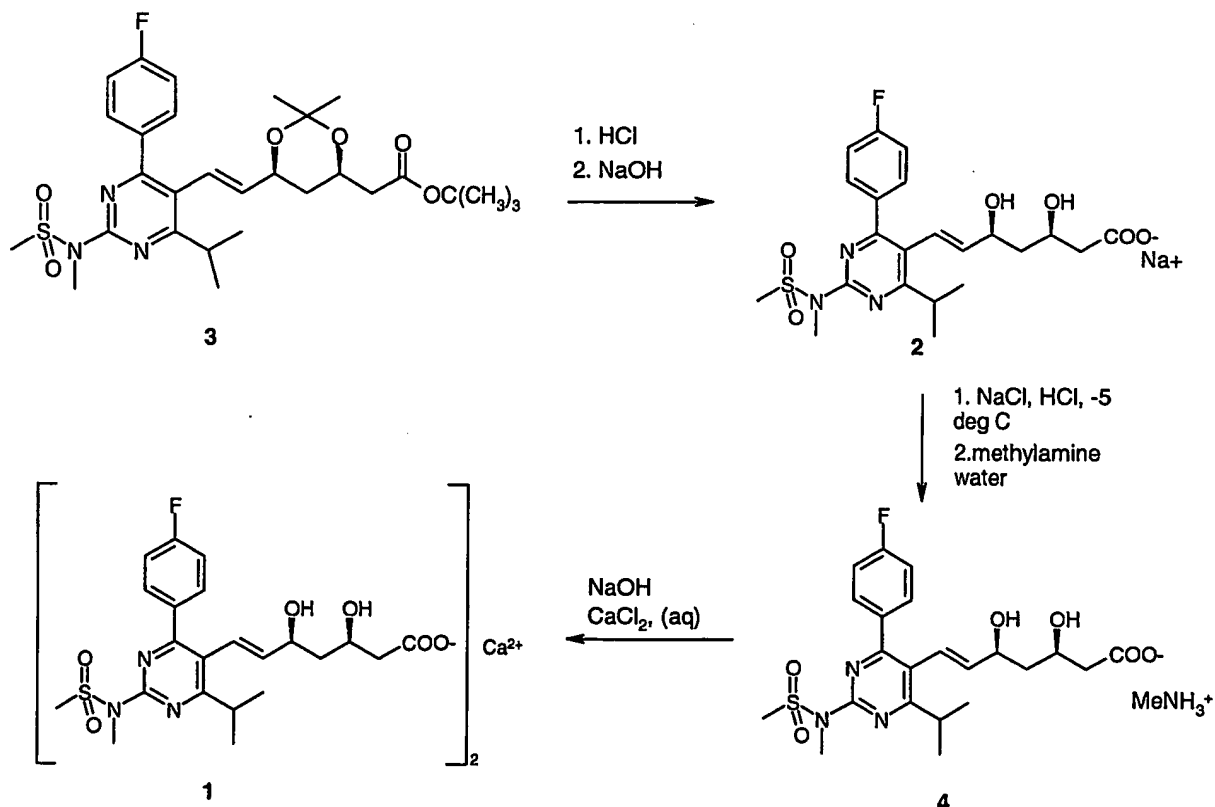
15 salt (2), as shown in Scheme 1 below. The calcium salt thus formed is then collected and dried and may be processed further as required.



Scheme 1

Our International Patent Application WO 00/49014 describes an alternative route to the calcium salt (1), also via the sodium salt (2), from the compound BEM (3), which is

5 exemplified as shown in Scheme 2 below:



Scheme 2

As described in WO 00/49014, the transformation from BEM (3) to the calcium salt (1) may be carried out via the methylamine salt (4) as shown in Scheme 2. Isolation of this intermediate crystalline methylamine salt allows purification by recrystallisation before final formation of the (amorphous) calcium salt.

5 Our co-pending application WO 2004/014872 describes an improved process for isolation of the calcium salt from a water soluble salt, such as the transformation from the methylamine salt (4) to the calcium salt (1) in Scheme 2 above, wherein the improvement comprises adjustment of time and temperature parameters such that optimal physical form of the product is obtained.

10 We have surprisingly discovered an improvement to the process of manufacturing the calcium salt, which results in improved overall yield and a reduced number of steps to effect the transformation from BEM (3) to the calcium salt (1), whereby the step of isolating an intermediate salt is avoided. Surprisingly the quality of the resultant calcium salt product is not adversely affected. The process of this invention is also applicable to alkyl esters of the
15 agent other than the tertiary-butyl ester, BEM (3).

According to the present invention there is provided an improved process for the formation of (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid calcium salt, which comprises the steps a) to g):

- 20 a) reaction of a (1-6C)alkyl ester of (*E*)-(6-{2-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]vinyl}(4*R*,6*S*)-2,2-dimethyl[1,3]dioxan-4-yl)acetic acid in a water miscible organic solvent with aqueous acid at an elevated temperature;
- b) reaction of the resulting solution with an aqueous alkali metal hydroxide and
25 optionally washing the resulting aqueous alkali metal salt solution with a suitable organic solvent;
- c) adjustment of the pH of the resulting solution to between pH6 and pH11;
- d) removal of the water miscible organic solvent;
- e) optional filtration of the resulting mixture;
- 30 f) addition of a water soluble calcium salt to the filtrate so as to form (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid calcium salt; and
- g) isolation of the product of step f).

It will be appreciated that this process achieves the conversion of the ester to the calcium salt (1) without isolation of an intermediate salt of the acid.

Step a)

5 Suitable solvents for step a) are in general any water miscible organic solvent; for example solvents such as acetonitrile and acetone. A preferred solvent is acetonitrile.

 Suitable aqueous acids are acids whose calcium salt is water soluble so that it is not precipitated in Step f). In one embodiment, the aqueous acid is hydrochloric acid. In one aspect of this embodiment, the aqueous hydrochloric acid is approximately 0.1M. In another
10 aspect of this embodiment, the aqueous hydrochloric acid is \leq about 0.1M. Conveniently the aqueous hydrochloric acid is $<0.05M$, for example 0.02M.

 Suitably, the reaction of the (1-6C)alkyl ester of the Agent with aqueous acid is carried out between 30 and 50°C, conveniently between 35 and 40°C.

 More suitably, the (1-6C)alkylester of the Agent, dissolved in acetonitrile at 35°C is
15 reacted with aqueous hydrochloric acid at 35°C.

 Suitable (1-6C)alkyl esters of the Agent are, for example methyl, ethyl, propyl, isopropyl, n-butyl, iso-butyl, pentyl or hexyl esters. BEM is a preferred example of a (1-6C)alkyl ester of (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-
[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid.

20 The starting material BEM may be made as described in WO 00/49014. Analogues of BEM may be made by analogous processes, as illustrated in the Examples hereinafter.

Step b)

 Step b) may be carried out at a temperature of between approximately 10°C and
25 approximately 40°C. Conveniently, step b) is carried out at ambient temperature, which will generally be understood to mean 20-25°C, conveniently approximately 25°C.

 Suitably the aqueous alkali metal hydroxide is aqueous potassium hydroxide or aqueous sodium hydroxide.

 In one embodiment, the aqueous alkali metal hydroxide is sodium hydroxide. In this
30 embodiment, suitably the aqueous sodium hydroxide is about 1M and sufficient quantity is added to form the sodium salt (2). It will be appreciated that the sodium salt (2) is not isolated and that the product of step b) is an aqueous sodium salt solution. It will also be appreciated that this aqueous sodium salt solution also contains acetonitrile.

The aqueous alkali metal salt solution may be washed with toluene, or another suitable organic solvent to remove unreacted (1-6C)alkyl ester of the Agent, such as BEM (3), or other unwanted minor components if required, prior to carrying out step c). Suitable organic solvents for this washing step are in general organic solvents which are immiscible in water but miscible with the water miscible organic solvent used in step a). When the water miscible organic solvent in step a) is acetonitrile, suitable organic solvents for the washing step are ester, ether and hydrocarbon solvents known in the art. Examples of such suitable solvents are xylene (hydrocarbon solvent), methyl-t-butylether (MTBE) (ether solvent) and ethyl acetate (ester solvent). The toluene or other suitable organic solvent may conveniently be removed from the process by phase separation. Any solvent remaining after phase separation may be removed in Step d). Preferably the solvent is toluene.

In one embodiment, the aqueous alkali metal salt is an aqueous sodium salt. In this embodiment, in step b), the aqueous sodium salt solution is washed with a suitable organic solvent. In one aspect of this embodiment, the aqueous sodium salt solution is washed with toluene, xylene, MTBE or ethyl acetate. In a further aspect of this embodiment, the aqueous sodium salt solution is washed with toluene or xylene. In a further aspect of this embodiment, the aqueous sodium salt solution is washed with toluene. In a further aspect of this embodiment, the aqueous sodium salt solution is washed with MTBE. In a further aspect of this embodiment, the aqueous sodium salt solution is washed with ethyl acetate.

In another embodiment, in step b), the aqueous sodium salt solution is not washed with a suitable organic solvent.

In an alternative embodiment of this invention, the aqueous alkali metal hydroxide is potassium hydroxide. It will be appreciated that in this embodiment, the potassium salt equivalent of the sodium salt (2) is formed as a result. In this embodiment, suitable temperatures, concentrations of potassium hydroxide and washing solvents are those described as suitable for sodium hydroxide hereinbefore.

Step c)

Adjustment of the aqueous solution to pH 6 - 11 is suitably carried out by addition of hydrochloric acid, for example 0.02 to 1M aqueous hydrochloric acid. In one embodiment, the solution is adjusted to pH 8-11. In another embodiment, the solution is adjusted to pH 9-11, for example about pH 9-10.5. Suitably, the solution is adjusted to about pH 9-10.5 using

≤0.1M hydrochloric acid. More suitably, the solution is adjusted to about pH 10.5 using about 0.1M hydrochloric acid. Preferably the solution is adjusted to about pH9, suitably using 0.02M aqueous hydrochloric acid. Other inorganic acids known in the art may also be used, provided the calcium salt of the inorganic acid is water soluble so that it is not precipitated in
5 Step f).

Step d)

The water miscible organic solvent (and residual amounts of any organic solvent used as a wash in step b) above), may generally be removed by distillation, conveniently carried
10 out under vacuum.

When the water miscible organic solvent is acetonitrile, the distillation is suitably carried out for example using a vacuum of ≤55 mBar, and a temperature of ≤45 °C. Conveniently, the vacuum is about 52 mBar and the temperature is about 33°C. It will be appreciated by those skilled in the art that water may be azeotropically removed with the
15 acetonitrile during the distillation and that it may therefore be desirable to add further water to the mixture during the distillation process. A suitable method for carrying out the distillation is provided in the accompanying non-limiting Example.

Step e)

20 Filtration of the mixture resulting from step d) removes any unreacted starting material or insoluble impurities which may have precipitated during the distillation process of step d). It will be appreciated that water may be used to wash the filter. Any filter known in the art to be suitable may be used. Conveniently at a manufacturing scale, a GaF filter may be used (for example, a GAF filter E6-1825, manufactured by "Haywood Industrial Products).

25 It will be appreciated that this filtration is not always necessary and may be omitted.

Step f)

Generally, the water soluble calcium salt is suitably any such salt whose counter-ion forms a water soluble salt with sodium, such that it is easily removed by washing the product
30 after isolation in step g). Suitable water soluble calcium salts include calcium chloride, calcium bromide and calcium acetate. More suitably, calcium chloride or calcium bromide is used.

In one embodiment, the water soluble calcium salt is calcium chloride.

In this embodiment, calcium chloride is conveniently provided as its dihydrate form and is suitably added to the filtrate as an aqueous solution. A slight excess of calcium chloride may be used, for example 0.6 molar equivalents compared to the Agent. The calcium chloride is suitably added as a 0.1 g/ml aqueous solution. The temperature of the reaction mixture is suitably maintained at 32-43°C, more suitably at approximately 40°C, during the addition process. The rate of addition of calcium chloride may be adjusted such that the temperature of the reaction mixture is so maintained. Suitably the calcium chloride is added over 15-30 minutes. The mixture may be maintained at the addition temperature for a period (herein referred to as the 'hold time') before isolation of the calcium salt. In one embodiment, the hold time is at least 10 minutes. In another embodiment the hold time is at least 20 minutes. In a further embodiment the hold time is at least 30 minutes.

Step g)

Isolation of the calcium salt may conveniently be carried out by filtration, conveniently at about 20°C (herein referred to as the "filtration temperature"). The mixture may be maintained at the filtration temperature for a period before filtration is carried out, for example for 10 to 20 minutes, conveniently for 15 minutes. It will be appreciated that water may be used to wash the filtrate.

According to the present invention there is provided an improved process for the formation of (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid calcium salt, which comprises the steps a) to g):

- a) reaction of tert-butyl (*E*)-(6-{2-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]vinyl}(4*R*,6*S*)-2,2-dimethyl[1,3]dioxan-4-yl)acetate (BEM) in acetonitrile with aqueous hydrochloric acid at an elevated temperature;
- b) reaction of the resulting solution with aqueous sodium hydroxide;
- c) adjustment of the pH of the resulting solution to between pH6 and pH11;
- d) removal of acetonitrile;
- e) filtration of the resulting mixture;
- f) addition of calcium chloride to the filtrate so as to form (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid calcium salt; and

g) isolation of the product of step f).

In a further aspect of the invention there is provided an improved process for the formation of (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-

5 [methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid calcium salt, which comprises the steps a), b) c), d), f) and g) as described hereinbefore.

According to the present invention is provided an improved process for the formation of (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-

10 yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid calcium salt, which comprises the steps a') to g):

a') reaction of a (1-6C)alkyl ester of (*E*)-(6-{2-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]vinyl}(4*R*,6*S*)-2,2-dimethyl[1,3]dioxan-4-yl)acetic acid in acetonitrile with aqueous hydrochloric acid at an elevated temperature;

b) reaction of the resulting solution with aqueous sodium hydroxide;

15 c) adjustment of the pH of the resulting solution to between pH6 and pH11;

d) removal of acetonitrile;

e) filtration of the resulting mixture;

f) addition of calcium chloride to the filtrate so as to form (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-

20 enoic acid calcium salt; and

g) isolation of the product of step f).

In a further aspect of the invention is provided an improved process for the formation of (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid calcium salt, which comprises the steps a'), b) c),

25 d), f) and g) as described hereinbefore.

In a further embodiment, the present invention provides an improved process for the formation of (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-

[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid

30 calcium salt, which comprises the steps a) to g):

a) reaction of tert-butyl (*E*)-(6-{2-[4-(4-fluorophenyl)-6-isopropyl-2-

[methyl(methylsulfonyl)amino]pyrimidin-5-yl]vinyl}(4*R*,6*S*)-2,2-dimethyl[1,3]dioxan-4-yl)acetate (BEM) in acetonitrile with aqueous hydrochloric acid at 35-40°C;

- b) reaction of the resulting solution with 1M sodium hydroxide at ambient temperature and optionally washing the resulting aqueous sodium salt solution with a suitable organic solvent;
- c) adjustment of the pH of the resulting solution to about pH9 by addition of <0.05M aqueous hydrochloric acid;
- 5 d) removal of acetonitrile by distillation at 50-55mBar and 30-35°C;
- e) filtration of the resulting mixture;
- f) addition of an aqueous solution of calcium chloride dihydrate to the filtrate so as to form (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid calcium salt, at 32-43°C; and
- 10 g) isolation of the product of step f) by filtration at about 20°C.

In a further embodiment, the present invention provides an improved process for the formation of (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid calcium salt, which comprises the steps a') to g):

15

- a') reaction of a (1-6C)alkyl ester of (*E*)-(6-{2-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]vinyl}(4*R*,6*S*)-2,2-dimethyl[1,3]dioxan-4-yl)acetic acid in acetonitrile with aqueous hydrochloric acid at 35-40°C;
- b) reaction of the resulting solution with 1M sodium hydroxide at ambient temperature and optionally washing the resulting aqueous sodium salt solution with a suitable organic solvent;
- 20 c) adjustment of the pH of the resulting solution to about pH9 by addition of <0.05M aqueous hydrochloric acid;
- d) removal of acetonitrile by distillation at 50-55mBar and 30-35°C;
- 25 e) filtration of the resulting mixture;
- f) addition of an aqueous solution of calcium chloride dihydrate to the filtrate so as to form (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid calcium salt, at 32-43°C; and
- g) isolation of the product of step f) by filtration at about 20°C.

In a further embodiment, the present invention provides an improved process for the formation of (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid calcium salt, which comprises the steps a) to g):

30

- a) reaction of *tert*-butyl (*E*)-(6-{2-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]vinyl}(4*R*,6*S*)-2,2-dimethyl[1,3]dioxan-4-yl)acetate (BEM) in acetonitrile with aqueous hydrochloric acid at 35-40°C;
- b) reaction of the resulting solution with 1M sodium hydroxide at ambient temperature
5 and optionally washing the resulting aqueous sodium salt solution with a suitable organic solvent;
- c) adjustment of the pH of the resulting solution to about pH 9-10.5 using ≤ 0.1 M aqueous hydrochloric acid
- d) removal of acetonitrile by distillation at 50-55mBar and 30-35°C;
- 10 e) filtration of the resulting mixture;
- f) addition of an aqueous solution of calcium chloride dihydrate to the filtrate so as to form (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid calcium salt, at 32-43°C; and
- g) isolation of the product of step f) by filtration at about 20°C.

15 In a further embodiment, the present invention provides an improved process for the formation of (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid calcium salt, which comprises the steps a') to g):

- a') reaction of a (1-6C)alkyl ester of (*E*)-(6-{2-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]vinyl}(4*R*,6*S*)-2,2-dimethyl[1,3]dioxan-4-yl)acetic acid in acetonitrile with aqueous hydrochloric acid at 35-40°C;
- 20 b) reaction of the resulting solution with 1M sodium hydroxide at ambient temperature and optionally washing the resulting aqueous sodium salt solution with a suitable organic solvent;
- 25 c) adjustment of the pH of the resulting solution to about pH 9-10.5 using ≤ 0.1 M aqueous hydrochloric acid
- d) removal of acetonitrile by distillation at 50-55mBar and 30-35°C;
- e) filtration of the resulting mixture;
- f) addition of an aqueous solution of calcium chloride dihydrate to the filtrate so as to
30 form (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid calcium salt, at 32-43°C; and
- g) isolation of the product of step f) by filtration at about 20°C.

In a further embodiment, the present invention provides an improved process for the formation of (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid calcium salt, which comprises the steps a') to g):

- 5 a') reaction of a (1-6*C*)alkyl ester of (*E*)-(6-{2-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]vinyl}(4*R*,6*S*)-2,2-dimethyl[1,3]dioxan-4-yl)acetic acid in acetonitrile with aqueous hydrochloric acid at 35-40°C;
- b) reaction of the resulting solution with 1M sodium hydroxide at ambient temperature and optionally washing the resulting aqueous sodium salt solution with a suitable
- 10 hydrocarbon, ester or ether solvent;
- c) adjustment of the pH of the resulting solution to about pH 9-10.5 using ≤0.1M aqueous hydrochloric acid
- d) removal of acetonitrile by distillation at 50-55mBar and 30-35°C;
- e) filtration of the resulting mixture;
- 15 f) addition of an aqueous solution of calcium chloride dihydrate to the filtrate so as to form (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid calcium salt, at 32-43°C; and
- g) isolation of the product of step f) by filtration at about 20°C.

In a further embodiment, the present invention provides an improved process for the formation of (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid calcium salt, which comprises the steps a') to g):

- 20 a') reaction of a (1-6*C*)alkyl ester of (*E*)-(6-{2-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]vinyl}(4*R*,6*S*)-2,2-dimethyl[1,3]dioxan-4-yl)acetic acid in acetonitrile with aqueous hydrochloric acid at 35-40°C;
- 25 b) reaction of the resulting solution with 1M sodium hydroxide at ambient temperature and optionally washing the resulting aqueous sodium salt solution with toluene, xylene, MTBE or ethylacetate;
- c) adjustment of the pH of the resulting solution to about pH 9-10.5 using ≤0.1M
- 30 aqueous hydrochloric acid
- d) removal of acetonitrile by distillation at 50-55mBar and 30-35°C;
- e) filtration of the resulting mixture;

- f) addition of an aqueous solution of calcium chloride dihydrate to the filtrate so as to form (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid calcium salt, at 32-43°C; and
- g) isolation of the product of step f) by filtration at about 20°C.

5 In a further embodiment, the present invention provides an improved process for the formation of (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid calcium salt, which comprises the steps a') to g):

- a') reaction of a (1-6C)alkyl ester of (*E*)-(6-{2-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]vinyl}(4*R*,6*S*)-2,2-dimethyl[1,3]dioxan-4-yl)acetic acid in acetonitrile with aqueous hydrochloric acid at 35-40°C;
- 10 b) reaction of the resulting solution with 1M sodium hydroxide at ambient temperature and optionally washing the resulting aqueous sodium salt solution with toluene;
- c) adjustment of the pH of the resulting solution to about pH 9-10.5 using ≤ 0.1 M
- 15 aqueous hydrochloric acid
- d) removal of acetonitrile by distillation at 50-55mBar and 30-35°C;
- e) filtration of the resulting mixture;
- f) addition of an aqueous solution of calcium chloride dihydrate to the filtrate so as to form (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid calcium salt, at 32-43°C; and
- 20 g) isolation of the product of step f) by filtration at about 20°C.

In a further embodiment, the present invention provides an improved process for the formation of (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-

25 [methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid calcium salt, which comprises the steps a') to g):

- a') reaction of a (1-6C)alkyl ester of (*E*)-(6-{2-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]vinyl}(4*R*,6*S*)-2,2-dimethyl[1,3]dioxan-4-yl)acetic acid in acetonitrile with aqueous hydrochloric acid at 35-40°C;
- 30 b) reaction of the resulting solution with 1M sodium hydroxide at ambient temperature and washing the resulting aqueous sodium salt solution with a suitable hydrocarbon, ester or ether solvent;

- c) adjustment of the pH of the resulting solution to about pH 9-10.5 using $\leq 0.1M$ aqueous hydrochloric acid
- d) removal of acetonitrile by distillation at 50-55mBar and 30-35°C;
- e) filtration of the resulting mixture;
- 5 f) addition of an aqueous solution of calcium chloride dihydrate to the filtrate so as to form (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid calcium salt, at 32-43°C; and
- g) isolation of the product of step f) by filtration at about 20°C.

In a further embodiment, the present invention provides an improved process for the
 10 formation of (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid calcium salt, which comprises the steps a') to g):

- a') reaction of a (1-6C)alkyl ester of (*E*)-(6-{2-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]vinyl}(4*R*,6*S*)-2,2-dimethyl[1,3]dioxan-4-
 15 yl)acetic acid in acetonitrile with aqueous hydrochloric acid at 35-40°C;
- b) reaction of the resulting solution with 1M sodium hydroxide at ambient temperature and washing the resulting aqueous sodium salt solution with toluene, xylene, MTBE or ethylacetate;
- c) adjustment of the pH of the resulting solution to about pH 9-10.5 using $\leq 0.1M$
 20 aqueous hydrochloric acid
- d) removal of acetonitrile by distillation at 50-55mBar and 30-35°C;
- e) filtration of the resulting mixture;
- f) addition of an aqueous solution of calcium chloride dihydrate to the filtrate so as to form (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-
 25 yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid calcium salt, at 32-43°C; and
- g) isolation of the product of step f) by filtration at about 20°C.

In a further embodiment, the present invention provides an improved process for the
 formation of (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid
 30 calcium salt, which comprises the steps a') to g):

- a') reaction of a (1-6C)alkyl ester of (*E*)-(6-{2-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]vinyl}(4*R*,6*S*)-2,2-dimethyl[1,3]dioxan-4-
 yl)acetic acid in acetonitrile with aqueous hydrochloric acid at 35-40°C;

- b) reaction of the resulting solution with 1M sodium hydroxide at ambient temperature and washing the resulting aqueous sodium salt solution with toluene;
- c) adjustment of the pH of the resulting solution to about pH 9-10.5 using ≤ 0.1 M aqueous hydrochloric acid
- 5 d) removal of acetonitrile by distillation at 50-55mBar and 30-35°C;
- e) filtration of the resulting mixture;
- f) addition of an aqueous solution of calcium chloride dihydrate to the filtrate so as to form (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid calcium salt, at 32-43°C; and
- 10 g) isolation of the product of step f) by filtration at about 20°C.

In a further embodiment, the present invention provides an improved process for the formation of (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid calcium salt, which comprises the steps a') to g) as described in any aspect or embodiment
15 hereinbefore or hereinafter, wherein, in step b), potassium hydroxide is used instead of sodium hydroxide.

The process of the invention generally results in improved overall percentage yield (starting from BEM or other (1-6C)alkyl ester) and a reduced number of steps in comparison
20 with the processes known in the art. It will be appreciated that a higher percentage yield may provide a significant cost benefit when manufacture is taking place on a commercial scale. The reduced number of steps in the process of the invention results in fewer operational processes during the manufacture, which may translate into a more robust process. The reduced number of steps in the process of the invention involves reduced handling of material,
25 which may result in less opportunity for degradation or contamination of the product. Also, certain chemical reagents are no longer required and the total amount of waste and/or effluent is reduced, providing an environmental benefit.

A further aspect of the invention provides the compound (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-
30 enoic acid calcium salt made by the process steps a) to g) as hereinbefore described.

A further aspect of the invention provides the compound (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-

enoic acid calcium salt made by the process steps a') to g) as described in any aspect or embodiment hereinbefore.

Therefore a further aspect of the invention provides a product obtainable by the process of the present invention.

Another aspect of the invention provides a product obtained by the process of the present invention.

It will be appreciated that the process of the current invention could be applied to make alternative salts of the Agent, such as the magnesium salt by use of a suitable magnesium salt in step f), such as magnesium chloride. Such a salt thus obtained could be converted by processes known in the art into the calcium salt (1). Thus in another aspect of the invention, is provided a process for making the magnesium salt of the Agent, comprising the steps a) to g) as hereinbefore described wherein, in step f) a water soluble magnesium salt (such as magnesium chloride) is added instead of a water soluble calcium salt (such as calcium chloride).

The invention is further illustrated by the following examples.

Example 1

BEM (20.0g) was dissolved in acetonitrile (140ml) at 40°C, then cooled to 35°C before gradual addition of hydrochloric acid (0.02M, 35ml) at 35°C. The resulting solution was stirred at 35°C until the reaction was complete then cooled to 25°C. Sodium hydroxide (1.0M, 38ml) was added at 25°C and the resulting mixture stirred at this temperature until the reaction was complete. Aqueous hydrochloric acid (1M) was added to adjust the pH of the solution to pH9. The solution was distilled under reduced pressure (52mBar, $\leq 40^{\circ}\text{C}$) until approximately 100ml of acetonitrile/water had been removed. Water (100ml) was added and distillation continued until a further 100ml of acetonitrile/water had been removed. The resulting mixture was filtered through a filter pad, the filter washed with water (30ml) and the filtrates heated to 40°C before addition of a solution of calcium chloride dihydrate (3.07g) in water (29.5ml) over 20min, maintaining the reaction mixture at 38-41°C. The reaction mixture was stirred for a further 15min at 40°C, then cooled to 20°C and stirred at this temperature for a further 15min. The resulting suspension was filtered, washed with water (3 x 50ml) and dried to give (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-

[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid calcium salt (15.8g, 84% yield).

Example 2

- 5 The synthesis of analogues of BEM is illustrated below for the iso-propyl analogue. Other analogues can be made by similar procedures.

iso-Propyl (E)-(6-{2-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]vinyl}(4*R*,6*S*)-2,2-dimethyl[1,3]dioxan-4-yl)acetate

- 10 Sodium bis(trimethylsilyl)amide (80.47 mL, 1.0M in THF) was added dropwise to a cooled solution of diphenyl [4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-ylmethyl] phosphine oxide (40.43 g, 75 mmol) in THF (477.1 mL) at -65°C over 30 minutes, maintaining the temperature at -65°C. Isopropyl- 2-[(4*R*,6*S*)-6-formyl-2,2-dimethyl-1,3-dioxan-4-yl]acetate in toluene (21.68 g) was added dropwise to the solution
- 15 over 35 minutes, maintaining the temperature at -65°C. The contents of the vessel were kept at -65°C for 15 minutes, then allowed to warm evenly to 10°C over 80 minutes. Water (40.4 mL) followed by acetic acid (6.87 g, 114 mmol) were added to give a two phase light yellow solution. The batch was then distilled at atmospheric pressure to remove ~ 485 mL of distillates. This solution was washed sequentially with water (84 mL), 7.0% w/w sodium
- 20 bicarbonate (92.6 g), 1.8% w/w sodium bicarbonate (91.1 g) and water (63.5 mL). The resulting organic phase was distilled under vacuum at 270 mbar to leave ~ 95 mL of solution in the distillation flask (removing ~ 229mL of distillates). Methanol (202 mL) at 50°C was charged to the flask and the solution distilled at atmospheric pressure, removing ~ 134 mL of distillates. A further portion of methanol (229 mL) at 50°C was added to the solution and the
- 25 batch cooled to 40°C over 30 minutes. The batch was cooled to 25°C over 30 minutes, 0-5°C over 30 minutes, then chilled to -8°C over 20 minutes and kept at this temperature for 30 minutes. The solid was collected by vacuum filtration, washed with 2 portions of cooled (-8°C) methanol (2 x 80.6 mL) then dried in a vacuum oven at 50°C, 200 mbar, yield = 28.9 g (68.3%).
- 30 ¹H NMR δ: 1.15 (q, 1H) 1.24 (dd, 6H) 1.27 (dd, 6H) 1.40 (s, 3H) 1.49 (s, 3H) 1.55 (dt, 1H) 2.34 (dd, 1H) 2.50 (dd, 1H) 3.38 (spt, 1H) 3.51 (s, 3H) 3.57 (s, 3H) 4.32 (m, 1H) 4.43 (m, 1H) 5.04 (spt, 1H) 5.47 (dd, 1H) 6.52 (d, 1H) 7.08 (t, 2H) 7.65 (dd, 2H)

Isopropyl- 2-[(4R,6S)-6-formyl-2,2-dimethyl-1,3-dioxan-4-yl]acetate

Chlorine gas (2469.6 mL, 118 mmol) was charged to toluene (373.3 mL, 16 rel vol) at -60°C . Dimethyl sulphide (11.67 mL, 121 mmol) was then added dropwise to the cooled solution over 30 minutes, keeping the contents at -60°C . After 30 minutes at this temperature, isopropyl 2-[(4R,6S)-6-hydroxymethyl-2,2-dimethyl-1,3-dioxan-4-yl]acetate (24.56 g, 95 mmol) in toluene (46.7 mL) was added dropwise to the vessel over 30 minutes, maintaining the internal temperature at -60°C . The reaction mixture was agitated at -60°C for 30 minutes followed by the dropwise addition of triethylamine (26.36 g, 261 mmol) over 30 minutes, allowing the internal temperature to rise to -50°C . The reaction mixture was then allowed to warm to 25°C evenly over 75 minutes. The resulting slurry was stirred at 25°C for 30 minutes, then water (77 mL) was added and the mixture agitated for 30 minutes. The aqueous layer was separated and the pH checked (pH should be between 7.5 and 8.5). The resulting organic portion was washed with water (23.3 mL) and the organic portion separated for vacuum distillation at 150 mbar. Distillation was continued until ~350 mL of toluene had been removed. Toluene (350 mL) was added to the flask and the vacuum distillation repeated at 150 mbar to remove ~350 mL of toluene. The resulting solution was transferred to a flask containing activated 4 angstrom molecular sieves and left at ambient temperature overnight. This solution was used directly for the coupling stage.

Iso-propyl 2-[(4R,6S)-6-hydroxymethyl-2,2-dimethyl-1,3-dioxan-4-yl]acetate

This compound may be made using the procedures described in EP0319847.

Analogues with different ester groups R may be made by a similar method.

Diphenyl [4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-ylmethyl] phosphine oxide

This compound can be made as described in Patent Application WO00/49014

Example 3: Procedure using wash in step b)

BEM (20.0g) was dissolved in acetonitrile (140ml) at 40°C , then cooled to 35°C before gradual addition of hydrochloric acid (0.02M, 35ml) at 35°C . The resulting solution was stirred at 35°C until the reaction was complete then cooled to 25°C . Further acetonitrile (8 ml) was added before sodium hydroxide (1.0M, 38ml) was added at 25°C and the resulting mixture stirred at this temperature until the reaction was complete. Aqueous hydrochloric

acid (0.1M) was added to adjust the pH of the solution to approximately pH10.5. Water was added so that the combined volume of water and hydrochloric acid (0.1M) (from the previous pH adjustment step) added was 100ml. Toluene (125 ml) was then added and the mixture stirred at 40°C for 30 minutes before it was allowed to settle for 1 hour at 40°C. The aqueous phase was then separated from the organic phase at 40°C. The aqueous phase was distilled under reduced pressure (53mBar, ≤40°C) until the volume was reduced to 135 ml. The resulting aqueous solution was filtered through a filter pad and the filter washed with water and combined with the aqueous reaction solution, such that the total volume of the resulting aqueous solution was 170 ml. This solution was heated to 40°C before addition of a solution of calcium chloride di-hydrate (3.05g) in water (29.5ml) over 20min, maintaining the reaction mixture at 38-41°C.

The reaction mixture was stirred for a further 15 min at 40°C, then cooled to 20°C and stirred at this temperature for a further 15min. The resulting suspension was filtered, washed with water (3 x 53ml) and dried to give (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-

[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid calcium salt (14.7g @100% strength, 85% yield).

¹H NMR δ: 1.21 (d+d, 6H) 1.32 (dt, 1H) 1.51 (dt, 1H) 2.00 (dd, 1H) 2.14 (dd, 1H) 3.42 (spt, 1H)* 3.45 (s, 3H) 3.54 (s, 3H) 3.77 (m, 1H) 4.21 (q, 1H) 5.53 (dd, 1H) 6.51 (dd, 1H) 7.27 (t, 2H) 7.71 (dd, 2H)

[The ¹H NMR was carried out as a 3% w/v solution in d⁶ DMSO (where d⁵ DMSO=2.51δ)].

*partially obscured

Claims

1. A process for the formation of (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid
5 calcium salt, which comprises the steps a) to g):
 - a) reaction of a (1-6C)alkyl ester of (*E*)-(6-{2-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]vinyl}(4*R*,6*S*)-2,2-dimethyl[1,3]dioxan-4-yl)acetic acid in a water miscible organic solvent with aqueous acid at an elevated temperature;
 - 10 b) reaction of the resulting solution with an aqueous alkali metal hydroxide and optionally washing the resulting aqueous alkali metal salt solution with a suitable organic solvent;
 - c) adjustment of the pH of the resulting solution to between pH6 and pH11;
 - d) removal of the water miscible organic solvent;
 - 15 e) optional filtration of the resulting mixture;
 - f) addition of a water soluble calcium salt to the filtrate so as to form (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid calcium salt; and
 - g) isolation of the product of step f).
- 20 2. A process as claimed in Claim 1 wherein the water miscible organic solvent is acetonitrile.
3. A process as claimed in Claim 1 or Claim 2 wherein in step a) the aqueous acid is
25 hydrochloric acid.
4. A process as claimed in any one of the preceding claims wherein step b) comprises: reaction of the resulting solution with aqueous sodium hydroxide and washing the resulting aqueous sodium salt solution with a suitable hydrocarbon, ester or ether solvent.
- 30 5. A process as claimed in any one of the preceding claims wherein the aqueous sodium salt solution is washed with toluene, xylene, MTBE or ethyl acetate.

6. A process as claimed in Claim 5 wherein the aqueous sodium salt solution is washed with toluene.

7. A process as claimed in any one of the preceding claims wherein the (1-6C)alkyl ester
5 is the tert-butyl ester.

8. A process as claimed in any one of the preceding claims wherein step a) is carried out at 35-40°C.

10 9. A process as claimed in any one of the preceding claims wherein step b) is carried out at ambient temperature.

10. A process as claimed in Claim 1 wherein in step b), the aqueous alkali metal hydroxide is potassium hydroxide.

15

11. A process as claimed in any one of the preceding claims wherein step c) comprises adjustment of the pH of the solution to about pH9-10.5 by addition of aqueous hydrochloric acid.

20 12. A process as claimed in any one of the preceding claims wherein step d) is carried out at a pressure of ≤ 55 mBar and a temperature of $\leq 45^\circ\text{C}$.

13. A process as claimed in any one of the preceding claims wherein in step f) the water soluble calcium salt is calcium chloride.

25

14. A process as claimed in any one of the preceding claims wherein in step f) the calcium salt is added at 32-43°C.

15. The compound (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-
30 [methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid calcium salt made by the process steps a) to g) as claimed in Claim 1.

16. The compound (*E*)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3*R*,5*S*)-3,5-dihydroxyhept-6-enoic acid calcium salt made by the process steps a) to g) as claimed in Claim 7.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2004/002373A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D239/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, INSPEC, COMPENDEX

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 521 471 A (SHIONOGI & CO) 7 January 1993 (1993-01-07) cited in the application	1-14
X	page 2, line 42 - line 45; examples 1,7	15,16
Y	WO 00/49014 A (DIORAZIO LOUIS JOSEPH ; TAYLOR NIGEL PHILIP (GB); ASTRAZENEC A UK LTD () 24 August 2000 (2000-08-24) cited in the application	1-14
X	page 1, line 15 - page 2, line 10; claim 9; example 7	15,16
X	WO 00/42024 A (ASTRAZENECA UK LTD ; TAYLOR NIGEL PHILLIP (GB)) 20 July 2000 (2000-07-20) claim 1; example 1	15,16



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

11 October 2004

Date of mailing of the international search report

22/10/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5618 Patentlaan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Seelmann, M

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB2004/002373

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0521471	A	07-01-1993	AT 197149 T	15-11-2000
			CA 2072945 A1	02-01-1993
			CY 2226 A	18-04-2003
			DE 69231530 D1	30-11-2000
			DE 69231530 T2	13-06-2001
			DK 521471 T3	05-02-2001
			EP 0521471 A1	07-01-1993
			ES 2153824 T3	16-03-2001
			GR 3035189 T3	30-04-2001
			HK 1011986 A1	13-07-2001
			HU 220624 B1	28-03-2002
			HU 61531 A2	28-01-1993
			JP 2648897 B2	03-09-1997
			JP 5178841 A	20-07-1993
			KR 9605951 B1	06-05-1996
			LU 91042 A9	24-11-2003
			NL 300125 I1	01-07-2003
			PT 521471 T	30-04-2001
			US RE37314 E1	07-08-2001
			US 5260440 A	09-11-1993
WO 0049014	A	24-08-2000	AU 760145 B2	08-05-2003
			AU 2557300 A	04-09-2000
			BR 0008301 A	22-01-2002
			CA 2362594 A1	24-08-2000
			CN 1145625 T	14-04-2004
			CZ 20012930 A3	14-11-2001
			EE 200100430 A	16-12-2002
			EP 1155015 A1	21-11-2001
			WO 0049014 A1	24-08-2000
			HU 0200301 A2	28-08-2002
			JP 2003518474 T	10-06-2003
			NO 20013994 A	16-10-2001
			NZ 513261 A	31-10-2003
			PL 350185 A1	18-11-2002
			SK 11832001 A3	07-01-2002
			TR 200102360 T2	21-12-2001
			US 2004049036 A1	11-03-2004
			ZA 200106370 A	04-11-2002
WO 0042024	A	20-07-2000	AU 762909 B2	10-07-2003
			AU 1882600 A	01-08-2000
			BR 9916786 A	16-10-2001
			CA 2356212 A1	20-07-2000
			CN 1333756 T	30-01-2002
			CZ 20012460 A3	17-10-2001
			EE 200100359 A	16-12-2002
			EP 1144389 A1	17-10-2001
			WO 0042024 A1	20-07-2000
			HU 0104828 A2	29-07-2002
			ID 29432 A	30-08-2001
			JP 2002539078 T	19-11-2002
			NO 20013368 A	05-09-2001
			NZ 512560 A	29-08-2003
			PL 348775 A1	17-06-2002
			SK 9632001 A3	03-12-2001
			TR 200101894 T2	21-12-2001
			US 2004009997 A1	15-01-2004

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB2004/002373

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0042024	A	US 6589959 B1 ZA 200105187 A	08-07-2003 23-09-2002
<hr/>			

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☒ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☒ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.